REMARKS/ARGUMENTS

I. Preliminary Remarks and Status of the Claims

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."** Also, for the Examiner's convenience, attached hereto as Appendix B, is a complete list of the claims upon entry of the instant amendment. Appendix B is entitled "**Clean copy of claims pending in U.S. Serial No. 09/604,325 after entry of amendment filed December 10, 2002**."

Claims 71-96 are under consideration in the instant application. These claims stand variously rejected under 35 U.S.C. §112 first paragraph and under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the invention. Applicants respectfully traverse the rejections.

II. Objections to Drawings and Specification

The Examiner pointed out that the application was filed with informal drawings and indicated that formal drawings will be required when the application is allowed. Applicants confirm that formal drawings will be furnished upon allowance of the application, and in the meantime the Applicants respectfully request that the requirement for the formal drawings be held in abeyance.

The application was objected to for failure to comply with the requirements of 37 C.F.R. §§1.821 through 1.825, for reciting figure numbers instead of sequence identifiers in the claims. Applicants have amended the claims to recite sequence identifiers and therefore request that the objection be withdrawn.

The office action further required that the status of various applications referenced in the specification by serial number be updated. The above-presented amendment updates the status of the parent non-provisional application and the updates the status of any U.S. patent application numbers referenced in the specification.

The specification was further objected to because the Brief Description of the Drawings failed to refer to Figures 24A, 24B, 29A, 29B, 42A, 42B, 42C, 42D, 44A, 44B, 44C, 56A and 56B. Applicants have presented an amendment herein above to address this objection. The title has also been amended in accordance with the amendment suggested by the Examiner.

III. Rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

Claims 71 to 96 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in such a way as to enable one skilled in the art with which it is most nearly connected, to make and/or use the invention. The Examiner alleges that the specification does not teach methods or working examples that stimulate the growth of melanocyte precursor cells in any subject by administration of SCF alone or in combination with a cytokine. It is the Examiner's position that "the skilled artisan would not be able to predict the effects of administration of a SCF polypeptide or SCF-cytokine composition since it cannot be determined from the specification . . . which specific melanocyte precursor cells in the body are being targeted for the stimulation of growth," and hence undue experimentation would be required to determine the efficacy of growth of melanocyte precursor cells in a subject by administration of a SCF or SCF-cytokine composition. The Examiner further states that the specification lacks methods or working examples that treat a pigmentation disorder and points to literature reports that delivery of proteins and peptides has unpredictable success. Applicants traverse the examiner's rejection of the claims of the instant application for lack of enablement.

Of the total claims 71-96, there are two independent method claims in the present case. In the first instance, claim 71 is directed to a method of stimulating the growth of melanocyte precursor cells in a human, and in the second instance, claim 75 is directed to a method of treating a pigmentation disorder. Both of these methods are characterized in that they require the step of administering to the human an effective amount of a human stem cell factor and optionally a pharmaceutically acceptable carrier. The specification expressly teaches that stem cell factor polypeptide can be used to treat numerous diseases including pigmentation disorders. For example, at page 27, lines 35-36 and 24-27, the specification expressly contemplates that "hypopigmentation disorders such as piebaldism and vitiligo" are disorders which "are treatable with SCF." Methods of formulating proteins into pharmaceutical

compositions and methods of delivering the same are expressly disclosed in the specification and also were well known to those of skill in the art at the time of filing the application.

Applicants submit that no undue experimentation will be required for practicing the methods claimed in the present application. At the time that the priority application was filed (10/16/89), while there may have been speculation in the art as to the factor or factors that may be responsible for hypopigmentation disorders such as vitiligo and piebaldism the identity of such factor(s) was unknown. However, the inventors identified a novel stem cell factor and recognized that this factor may be used to treat hypopigmentation disorders. The fact that a specific working example of such treatment is not present in the specification does not defeat the enablement of the claimed invention because once the present inventors had taught individuals of skill in the art that stem cell factor could be used to treat these disorders and had taught how to make and administer compositions comprising SCF, it became a matter of routine experimentation and optimization to administer such formulations to subjects suffering from such disorders. Such methods of administering SCF protein composition to a human patient in accordance with the methods of the present invention would be the antithesis of undue experimentation as laid out by the Federal Circuit in *In re Wands*.

In re Wands clearly instructed that enablement is not precluded by the necessity for some experimentation; indeed, it is inevitable that there may be some quantity of experimentation required. Nonetheless the key word is ***undue***, not experimentation. *In re Wands*, 8 USPQ2d 1400, 1404. The court went on to instruct that a considerable amount of experimentation is in fact permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.* Applying the standard articulated in *In re Wands*, the present specification provides a reasonable amount of guidance to one of skill in the art to who wants to employ a given SCF in methods of treating a pigmentation disorder as contemplated by the claims of the present invention. Thus, the invention is objectively enabled and nothing more is required to satisfy the first paragraph of §112. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

Subsequent to the discoveries and teachings of the present invention, those of skill in the art recognized that "SCF increases melanocyte proliferation, differentiation, survival,

chemotaxis and secretion as well as accumulation *in vivo,*" and that "SCF is essential to melanocyte proliferation and differentiation." (Kawakami et al., J. Invest. Dermatol. 114:471-478, 2002 at page 471). Others have shown that injection of recombinant human stem cell factor compositions "promote both the hyperplasia and the functional activation of human mast cells and melanocytes *in vivo* . . . . These findings also indicate that the interaction between SCF and its receptor represents a potential therapeutic target for regulating the numbers and functional activity of both mast cells and cutaneous melanocytes." (Costa *et al.*, *J Exp Med* 183(6):2681-6, 1996). In addition, Kawakami et al., confirm that a cytokine (TGFbeta) also is involved in melanocyte proliferation and differentiation (Kawakami et al., 2002, at page 476) and that "transforming growth factor b1 affect melanocyte precursor proliferation and differentiation in the presence of stem cell factor. . ." (see abstract on page 471).

In the face of the well-established law and the factual recognition in the specification that SCF is a factor involved in hypopigmentation disorders, Applicants respectfully submit that the Examiner's position in this case is inaccurate. The specification shows one of skill in the art the various sequences of stem cell factor, the specification further provides explicit teachings of methods of formulating pharmaceutical compositions and methods of delivering the same to a subject in need thereof. Applicants believe this guidance enables one of skill in the art to administer the SCF protein-based pharmaceutical compositions. A disclosure need not teach, and preferably should omit, what is well known to those of skill in the art. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Hence, Applicants believe the specification satisfies the enablement requirement of 35 U.S.C. §112, first paragraph. This is corroborated by the fact that studies by groups such as Kawakami et al., and Costa et al. have confirmed the efficacy of the treatment methods of the claimed invention.

There is no requirement that Applicants provide a list of specific amounts of formulations or to list the phenotypic effects that would be seen upon administration of the SCF formulations. Such formulaic recitations are merely recitations of results of working examples and there is a long-standing tenant that working examples are not required for an enabling disclosure. *In re Robins*, 166 USPQ 552 (CCPA 1970); *In re Borkowski*, 164 USPQ 642, 645 (CCPA 1970). The first paragraph of §112 requires nothing more than objective enablement. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). Thus, an example may be a "working" or a

"prophetic" example, indeed the specification need not contain an example at all if the invention is otherwise disclosed in such a manner that one of skill in the art will be able to practice it without undue experimentation. Again, the present invention provides a disclosure of how to make various SCF protein compositions; it also provides guidance on how one of skill in the art may produce such compositions in pharmaceutically acceptable carriers, methods of administering these compounds either alone or in combination with cytokines also are expressly taught by the specification.

The Examiner is correct in stating that the applicants have presented "experiments in the specification [which] monitor the numbers of numerous cell type." The numerous cell types referred to in the specification are stem cells either of a hematopoietic or a non-hematopoietic lineage. At the time the application was filed, those of skill in the art were well aware of the fact that melanocytes develop from melanocyte precursor stem cells. Monitoring the proliferation and differentiation of melanocyte precursor cells was known to those of skill in the art and thus it was well within the skill of artisans practiced in this field to conduct and compare the proliferation and differentiation of melanocyte precursor cells in the described assays as a matter of routine laboratory practice.

In view of the foregoing response, Applicants submit the rejections of the claims under 35 U.S.C. §112, first paragraph are overcome. Applicants request that the rejection be withdrawn and the claims be reconsidered for allowance.

IV. Rejections under 35 U.S.C. §112, second paragraph are overcome by the amendments and should be withdrawn.

The Examiner rejected claims 77 and 83-84 under 35 U.S.C. §112, second paragraph. More particularly, the Examiner rejected the claims for using the acronyms "IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, GM-CSF, CSF-1, IGF-1 and LIF." While Applicants believe that these acronyms are well known to those of skill in the art to render the claims sufficiently clear, in an effort to expedite the prosecution of this case to allowance, Applicants have replaced the abbreviations with the full names of the associated cytokines. These amendments do not add new matter. Briefly, throughout these claims the abbreviation "IL" has been replace with the term "interleukin," the abbreviation "EPO" has been

replaced with the term "erythropoietin," the term "G-CSF" has been replaced with "Granulocyte Colony-stimulating Growth Factor", the abbreviation "GM-CSF" has been replaced with the term "Granulocyte-Macrophage Colony-Stimulating Factor," the abbreviation "CSF-1" has been replaced with the term "Colony Stimulating Factor-1," the abbreviation "IGF-1" has been replaced with the term "Insulin-like Growth Factor-1," and the abbreviation "LIF" has been replaced with the term "Leukemic Inhibitory Factor."

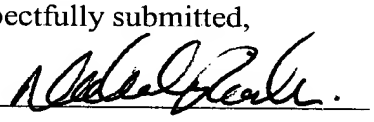
In view of the foregoing response, Applicants submit that the outstanding rejection of the claims under 35 U.S.C. §112, second paragraph is overcome. Applicants request that the rejection be withdrawn and the claims be reconsidered for allowance.

V. Concluding Remarks.

In view of the above amendments and remarks, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Applicants respectfully request a withdrawal of the rejections and an indication of allowance of the application. Should the Examiner have any questions regarding this submission, she is cordially invited to contact the undersigned representative.

Dated: January 10, 2003

Respectfully submitted,

By 

Nabeela R. McMillian
Registration No.: 43,363
MARSHALL, GERSTEIN & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300
Agent for Applicants

APPENDIX A
Version With Markings to Show Changes Made

In the Title:

Please amend the title as follows:

~~STEM CELL FACTOR~~ METHOD OF STIMULATING GROWTH OF MELANOCYTE PRECURSOR CELLS AND TREATMENT OF PIGMENTATION DISORDER BY ADMINISTERING STEM CELL FACTOR

In the Specification:

At paragraph 1, page 1, beginning line 3:

--This is a continuation application of U.S. application Serial No. 08/449,649, filed May 24, 1995, now abandoned, which is a divisional application of U.S. application Serial No. 08/172,329 filed December 21, 1993, now U.S. patent No. 6,218,148 issued April 17, 2001, which is a continuation of U.S. application Serial No. 07/982,255 filed November 25, 1992, now U.S. patent No. 6,204,363 issued March 20, 2001, which is a continuation of U.S. application Serial No. 07/684,535 filed April 10, 1991, now abandoned, which is a continuation-in-part of U.S. application Serial No. 07/589,701 filed October 1, 1990, now abandoned, which is a continuation-in-part application of U.S. application Serial No. 07/573,616 filed August 24, 1990, now abandoned, which is a continuation-in-part application of U.S. application Serial No. 07/537,198 filed June 11, 1990, now abandoned, which is a continuation-in-part application of U.S. application Serial No. 07/422,383 filed October 16, 1989, now abandoned, each of which are hereby incorporated by reference.--

--At page 24, paragraph 2, beginning line 21

--Isoforms of SCF are isolated using standard techniques such as the techniques set forth in commonly owned U.S. Serial No. 421,444, entitled Erythropoietin Isoforms, filed October 13, 1989, now abandoned, hereby incorporated by reference.--

At page 85, paragraph 1, beginning line 1:

--Vector pDSVE is described in commonly owned U.S. Ser. Nos. 025,344, now U.S. Patent No. 5,175,255 issued Dec. 12, 1992, and 152,045, now abandoned, hereby incorporated by reference. The vector portion of V19.8 and pDSVE.1 ColE1 origin of replication and ampicillin resistance gene and the SV40 origin of replication. This overlap may contribute to homologous recombination during the transformation process, thereby facilitating co-transformation.--

At page 182, paragraph 1, beginning line 1:

--Plasmid constructions for expression of numerous SCF analogs and fragments have been made. Site-directed mutagenesis had been used to prepare plasmids with initiating methionine codon followed by codons for amino acids 1 to 178, 173, 168, 166, 163, 162, 161, 160, 159 158 157 156 148 145 141 137, using the numbering of Figure 15C. The DNA for human SCF^{1-183} (Example 6B) was cloned into MP11 from Xba1 to BamH1. Phage from this cloning was used to transfect an *E. coli* dut^- ung^- strain, R21032. Single stranded M13 DNA was prepared from this strain and site-directed mutagenesis was performed (reference IL-2 patent). After the site-directed mutagenesis reactions, the DNAs were transformed into an *E. coli* dut^+ ung^+ strain, JM101. Clones were screened and sequences as described in copending U.S. application Serial No. 717,334, filed March 29, 1985. Plasmid DNA preps were made from positive clones and the SCF regions from Xba1 to BamH1 were cloned into pCFM1656 as described in copending U.S. patent application Serial No. 501,904, filed March 29, 1990, now abandoned. The oligonucleotides for each cloning were designed to substitute a stop codon for an amino acid codon tat the appropriate position for each analog.--

In the Brief Description of the Drawings

At page 11, lines 24-25

--Figure 24 shows the effect of recombinant rat SCF on curing the macrocytic anemia of Steel mice, as assessed by hematocrit analysis (24A) or mean red blood cell volume (24B).--

At page 12, lines 4-6

--Figure 29 shows the effect of recombinant human sequence SCF treatment of normal primates in increasing WBC count.

29A. expressed as white blood cells in [K/cmm]

29B. expressed as peripheral blood cells in [K/cmm].--

At page 12, lines 8-10

--Figure 30 shows the effect of recombinant human sequence SCF treatment of normal primates in increasing hematocrits (30B) and platelet numbers (30A).--

At page 13, lines 26-27

--Figures 42A-42D shows human SCF cDNA sequence obtained from the HT1080 fibrosarcoma cell line.--

At page 13, lines 33-34

--Figures 44A-44C shows human SCF cDNA sequence obtained from the 5637 bladder carcinoma cell line.--

At page 15, lines 10-11

--Figure 56 shows 5-FU effect on ACH+ cells in marrow (56A) and spleen (56B).--

In the Claims:

~~79~~ 71. [RENUMBERED] A method of stimulating growth of melanocyte precursor cells in a human, the method comprising the step of administering to the human, an amount of a human stem cell factor (SCF) polypeptide and optionally a pharmaceutically acceptable carrier.

~~80~~ 72. [RENUMBERED AND AMENDED] The method of claim ~~79~~ 71 wherein stem cell factor polypeptide selected is selected from the group consisting of amino acids 1-162, 1-164, and 1-165 as set out in SEQ ID NO: 46 ~~Figure 15C~~, said polypeptide optionally consisting of an N-terminal methionine.

~~81~~ 73. [RENUMBERED AND AMENDED] The method of claim ~~79~~ 71 wherein the stem cell factor polypeptide is selected from the group consisting of amino acids 1-100, 1-110, 1-120, 1-123, 1-127, 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 2-164, 2-165, 5-164, 11-164, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 as set out in SEQ ID NO: 61 ~~Figures 42A-C~~, said polypeptide optionally consisting of an N-terminal methionine.

~~82~~ 74. [RENUMBERED AND AMENDED] The method of claim ~~79~~ 71 wherein the stem cell factor polypeptide is selected from the group consisting of amino acids 1-152, 1-157, 1-160, 1-161, and 1-220 as set out in SEQ ID NO: 63 ~~Figure 44A-C~~, said polypeptide optionally consisting of an N-terminal methionine.

~~83~~ 75. [RENUMBERED] A method of treating a pigmentation disorder in a human, the method comprising the step of administering to the human, a therapeutically effective amount of a stem cell factor (SCF) polypeptide and optionally a pharmaceutically acceptable carrier.

~~84~~ 76. [RENUMBERED AND AMENDED] The method of claim ~~83~~ 75 wherein the stem cell factor polypeptide is selected from the group consisting of amino acids 1-162, 1-164, and 1-165 as set out in SEQ ID NO: 46 ~~Figure 15C~~, said polypeptide optionally consisting of an N-terminal methionine.

~~85~~ 77. [RENUMBERED AND AMENDED] The method of claim ~~83~~ 75 wherein the stem cell factor polypeptide is selected from the group consisting of amino acids 1-100, 1-110, 1-120, 1-123, 1-127, 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 2-164, 2-165, 5-164, 11-164, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 as set out in SEQ ID NO: 61 ~~Figures 42A-C~~, said polypeptide optionally consisting of an N-terminal methionine.

~~86~~ 78. [RENUMBERED AND AMENDED] The method of claim ~~83~~ 75 wherein the stem cell factor polypeptide is selected from the group consisting of amino acids 1-152, 1-

157, 1-160, 1-161, and 1-220 as set out in SEQ ID NO: 63 ~~Figure 44A-C~~, said polypeptide optionally consisting of an N-terminal methionine.

~~87~~ 79. [RENUMBERED AND AMENDED] The method of claim ~~79~~ 71 or [~~83~~] 75 wherein the stem cell factor is covalently conjugated to a water soluble polymer.

[~~88~~] 80. [RENUMBERED AND AMENDED] The method of claim [~~87~~] 79 wherein the water soluble polymer is polyethylene glycol.

[~~89~~] 81. [RENUMBERED AND AMENDED] The method of claim [~~79,~~] 71 or [~~83~~] 75 wherein the stem cell factor is co administered with at least one other cytokine.

[~~90~~] 82. [RENUMBERED AND AMENDED] The method of claim [~~87~~] 79 wherein the stem cell factor is co administered with at least one other cytokine.

[~~91~~] 83. [RENUMBERED AND AMENDED] The method of claim [~~89~~] 81 wherein one or more cytokines are selected from a group consisting of Interleukin-1 (IL-1), Interleukin-2 (IL-2), Interleukin-3 (IL-3), Interleukin-4 (IL-4), Interleukin-5 (IL-5), Interleukin-6 (IL-6), Interleukin-7 (IL-7), Interleukin-8 (IL-8), Interleukin-9 (IL-9), Interleukin-10 (IL-10), Interleukin-11 (IL-11), Interleukin-12 (IL-12), erythropoietin (EPO), Granulocyte Colony-stimulating Growth Factor (G-CSF), Macrophage Colony-Stimulating Factor (M-CSF), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Insulin-like Growth Factor-1 (IGF-1), and Leukemic Inhibitory Factor (LIF).

[~~92~~] 84. [RENUMBERED AND AMENDED] The method of claim [~~90~~] 82 wherein one or more cytokines are selected from a group consisting of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, M-CSF, GM-CSF, IGF-1, and LIF.

[~~93~~] 85. [RENUMBERED AND AMENDED] The method of claim [~~79~~] 71 wherein the pharmaceutically acceptable carrier is suitable for topical delivery.

[~~94~~] 86. [RENUMBERED AND AMENDED] The method of claim [~~79~~] 71 wherein the pharmaceutically acceptable carrier is suitable for oral delivery.

[~~95~~] 87. [RENUMBERED AND AMENDED] The method of claim [~~79~~] 71 wherein the pharmaceutically acceptable carrier is suitable for parenteral delivery.

[~~96~~] 88. [RENUMBERED AND AMENDED] The method of claim [~~79~~] 71 wherein the pharmaceutically acceptable carrier is suitable for pulmonary delivery.

[~~97~~] 89. [RENUMBERED AND AMENDED] The method of claim [~~79~~] 71 wherein the pharmaceutically acceptable carrier is suitable for nasal delivery.

[~~98~~] 90. [RENUMBERED AND AMENDED] The method of claim [~~83~~] 75 wherein the pharmaceutically acceptable carrier is suitable for topical delivery.

[~~99~~] 91. [RENUMBERED AND AMENDED] The method of claim [~~83~~] 75 wherein the pharmaceutically acceptable carrier is suitable for oral delivery.

[~~100~~] 92. [RENUMBERED AND AMENDED] The method of claim [~~83~~] 75 wherein the pharmaceutically acceptable carrier is suitable for parenteral delivery.

[~~101~~] 93. [RENUMBERED AND AMENDED] The method of claim [~~83~~] 75 wherein the pharmaceutically acceptable carrier is suitable for pulmonary delivery.

[~~102~~] 94. [RENUMBERED AND AMENDED] The method of claim [~~83~~] 75 wherein the pharmaceutically acceptable carrier is suitable for nasal delivery.

[~~103~~] 95. [RENUMBERED AND AMENDED] The method of claim [~~83~~] 75 wherein the pigmentation disorder is melanocytopenia.

[~~104~~] 96. [RENUMBERED AND AMENDED] The method of claim [~~83~~] 75 wherein the melanocytopenia is selected from the group consisting of vitilago and piebaldism.